33. (New) The method of claim 31, wherein the monoclonal antibody recognizes the peptide chain of about 27 kilodaltons, as determined by reducing SDS-PAGE.

34. (New) The method of claim 31, wherein the monoclonal antibody recognizes the peptide chain of about 29 kilodaltons, as determined by reducing SDS-PAGE.

35. (New) The method of claim 31, wherein the monoclonal antibody recognizes a human 8F4 polypeptide present on activated human $CD4^+$ T lymphocytes and activated human $CD8^+$ T lymphocytes.

36. (New) The method of claim 30, wherein the 8F4 inhibitory molecule is an 8F4 polypeptide.

REMARKS

Applicant has amended the cross reference section of the application, and has inserted appropriate section headings. A marked up version of the amended sections of the specification showing the amendments made herein is attached hereto as Exhibit A. In Exhibit A, the addition of text is indicated by quotation marks in view of the fact that the section headings are intended to be underlined in the text of the specification. The amendments to the specification do not introduce new matter as defined in 35 U.S.C. § 132.

Claims 1-20 were pending in this application. Claims 1-20 have been canceled without prejudice to Applicant's rights to pursue the subject matter of the claims in related patent applications. New claims 21-36 have been added. Claims 21-36, therefore, are currently pending in this application. A copy of the pending claims is attached hereto as Exhibit B.

The new claims are fully supported by the instant specification (see, *e.g.*, page 1, lines 10-17; page 4, line 31 to page 5, line 7; page 7, lines 1-46; page 8, lines 38-42; and the examples presented at pages 11-24), and do not represent new subject matter.

As will be discussed further below, scientific literature published after the filing date of the instant application corroborates the teachings of the presently claimed invention. The presently claimed invention (in claims 21-29) is directed to modulation of human T lymphocyte costimulation by administration of an ICOS[1] modulator, as taught in the specification at page 8, lines 38-42. The ICOS modulator of the claimed methods can be either a monoclonal antibody or an ICOS polypeptide. The presently claimed invention (in claims 30-36) is also drawn to a particular application of modulation of T lymphocyte costimulation: inhibition of organ transplant rejection by administering an ICOS inhibitory molecule which is either a monoclonal antibody or an ICOS polypeptide, as taught in the specification at page 7, lines 25-39.

First, Applicant invites the Examiner's attention to Özkaynak (Exhibit C). Özkaynak describes experiments in which modulation of ICOS by an anti-ICOS monoclonal antibody or an ICOS polypeptide results in modulation of T cell costimulation, as recited in claims 21-29. Özkaynak further demonstrates that in the context of an organ transplant, the administration of an ICOS inhibitory molecule to an organ transplant recipient leads to inhibition of organ transplant rejection, as recited in claims 30-36. More particularly, Özkaynak demonstrates that the expression of ICOS is upregulated, particularly in mononuclear cells, within five days of heart transplantation (see page 592 and Figure 1) in a mouse model system for graft rejection. Moreover, blocking ICOS costimulation activity by administering the ICOS monoclonal antibody 12A8, or by administering a soluble ICOS polypeptide, prolonged graft survival from approximately one week to almost three weeks (Figure 2). Similar prolongation of graft survival was observed in ICOS deficient mice, further evidencing a role for ICOS in rejection of the transplant. On a molecular level, the administration of the 12A8 antibody resulted in a reduction of cytokine and chemokine levels in the transplanted organ relative to untreated animals (Figure 4), indicating an inhibition of immune activation in the transplant.

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[1] It is noted that since the original filing date of the instant specification, the 8F4 polypeptide has come to be referred to in the literature as "ICOS" (Inducible T cell CO-Stimulator). As such, throughout this Amendment, Applicant will generally refer to 8F4 as "ICOS."

To summarize, the demonstration in Özkaynak that inhibition of ICOS by administration of an ICOS inhibitory molecule inhibits T cell costimulation provides support for claims 21-29, directed to a method of modulating T cell costimulation by contacting a human T lymphocyte with an ICOS modulator that is an ICOS polypeptide or a monoclonal antibody that recognizes a human ICOS polypeptide. Furthermore, the demonstration in Özkaynak of the consequence of inhibiting T cell costimulation in an organ transplant recipient, namely inhibition of organ transplant rejection, provides direct support for the subject matter of claims 30-36 directed to inhibition of organ transplant rejection by administration of an ICOS inhibitory molecule.

Applicant further draws the Examiner's attention to the Kroczek Declaration, attached hereto as Exhibit D, as further corroboration that T cell costimulation can be modulated by contacting T cells with an ICOS modulator selected from the group consisting of an ICOS polypeptide and a monoclonal antibody that recognizes a human ICOS polypeptide. The Kroczek Declaration is being submitted on even date herewith in a new continuation application of U.S. Application No. 09/509,283, the priority application of the present application. Like Özkaynak, the Kroczek Declaration describes a situation where T cell costimulation is modulated by contacting T cells with an ICOS modulator selected from the group consisting of an ICOS polypeptide and a monoclonal antibody that recognizes a human ICOS polypeptide. The Declaration discusses, *inter alia*, a paper by Gonzalo *et al.* (2001, "ICOS Is Critical for T Helper Cell-mediated Lung Mucosal Inflammatory Responses," Nature Immunol. 2(7):597-604), attached to the Declaration as Exhibit 2 ("Gonzalo"). In particular, the Kroczek Declaration notes that Gonzalo demonstrates that administration of an ICOS antibody or an ICOS polypeptide to an accpeted mouse model of asthma blocks molecular and cellular hallmarks of human asthma (see ¶ 5 of the Kroczek Declaration). On the molecular level, such administration reduces levels of inflammatory cytokines in the broncheoalveolar fluid ("BAL") and inhibits lymphocyte and eosinophil accumulation in the BAL of treated mice is also inhibited (see ¶¶ 7 and 8 of the Kroczek Declaration). Thus, Gonzalo provides further evidence that modulation of T lymphocyte costimulation can be achieved by contacting T cells with an ICOS modulator selected from the group consisting of an ICOS polypeptide and a monoclonal antibody that recognizes a

human ICOS polypeptide. The Kroczek Declaration, in addition to discussing the Gonzalo publication, describes in paragraphs 12 to 14 experiments demonstrating that ICOS-expressing cells are associated with lung inflammation that results in asthma in humans. This data supports the principle that T cell costimulation in humans will be modulated by contacting T cells with an ICOS modulator, as T cell costimulation is modulated in the mouse model discussed above.

Applicant submits that the teachings of the specification, for example at page 8, lines 38-42 and page 7, lines 1-46, fully enable the new claims 21-36, as evidenced by Özkaynak and by the Kroczek Declaration.

Entry of the amendments and remarks made herein is respectfully requested.

Respectfully submitted,

Date October 4, 2001

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By: Muna Abu-Shaar

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Enclosures